Study suggests how mosquitoes evolved an attraction to human scent

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Credit: CDC

The female mosquitoes that spread dengue and yellow fever didn't always rely on human blood to nourish their eggs. Their ancestors fed on furrier animals in the forest. But then, thousands of years ago, some of these bloodsuckers made a smart switch: They began biting humans and hitchhiked all over the globe, spreading disease in their wake.

"It was a really good evolutionary move," says Leslie B. Vosshall, the Robin Chemers Neustein Professor and head of the Laboratory of Neurogenetics and Behavior at The Rockefeller University, and a Howard Hughes Medical Institute investigator. "We provide the ideal lifestyle for mosquitoes. We always have water around for them to breed in, we are hairless, and we live in large groups."

To understand the evolutionary basis of this attraction, Vosshall and her colleagues examined the genes that drive some mosquitoes to prefer humans. Their findings, published in the November 13 issue of *Nature*, suggest that human-loving mosquitos are attracted to our scent. "They've acquired a love for human body odor, and that's a key step in specializing on us," she says.

The quest to understand what makes some mosquitoes prefer humans began in Rabai, Kenya. In the 1960s and 1970s, scientists visiting the region observed two distinct populations living just hundreds of meters apart. Black mosquitoes, a subspecies called Aedes aegypti formosus, tended to lay its eggs outdoors and preferred to bite forest animals. Their light-brown cousins, Aedes aegypti aegypti, tended to breed indoors in water jugs and mostly hunted humans. "We think we can get a glimpse of what happened thousands of years ago by looking at this little village in Kenya because the players are still there," Vosshall says.

In 2009, Carolyn McBride, who was a postdoc in Vosshall's laboratory at the time, and her co-investigators travelled to Rabai to see if these two groups still existed. The team used turkey basters to collect larvae from tree holes in the forest and sieved larvae from clay pots and metal cans inside people's homes. Back in the lab in New York they reared the insects and discovered that the observations that researchers had made years earlier seemed to hold true: The insects collected indoors tended to be light brown, and when given the option to bite humans or guinea pigs, they mostly choose humans. Those collected in the forest were black and

tended to prefer the laboratory guinea pigs.

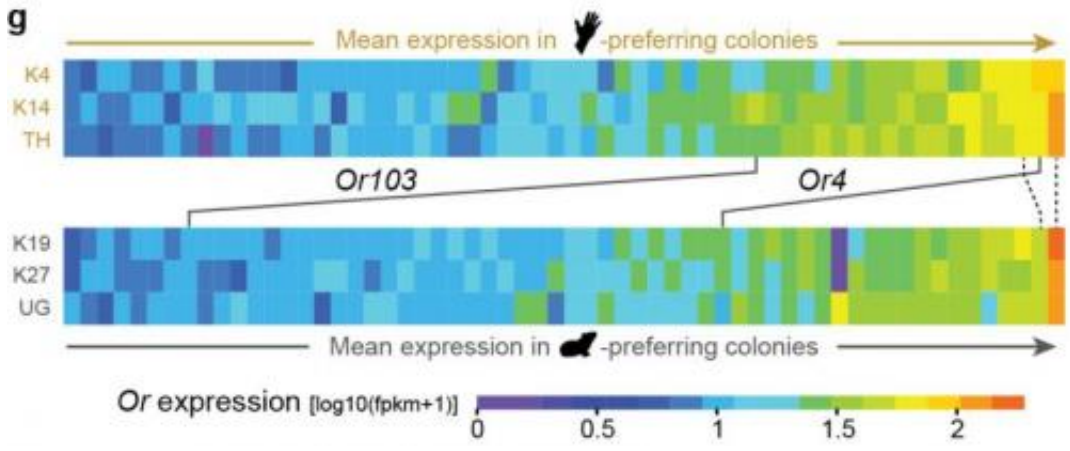
To zero in on the genes responsible for the human-loving mosquitoes' preference, the researchers crossbred the mosquitoes, creating thousands of genetically diverse grandchildren. And then they sorted those mosquitoes based on their odor preference and compared the two groups.

Researchers report that the yellow fever mosquito sustains its taste for human blood thanks in part to a genetic tweak that makes it more sensitive to human odor. The human-preferring 'domestic' form of the mosquito (right) contains a version of the odor-detecting gene AaegOr4 in its antennae that is highly attuned to sulcatone, a compound prevalent in human odor. The researchers found that this gene is more abundant and more sensitive in the domestic form than in its ancestral 'forest' form (left), which prefers the blood of non-human animals. Credit: Carolyn McBride, Department of Ecology and Evolutionary Biology and the Princeton Neuroscience Institute

"We knew that these mosquitoes had evolved a love for the way we smell," Vosshall says. So she and her colleagues looked specifically for genes that had higher levels of expression in the human-loving insects' antennae. These structures contain proteins called odorant receptors that pick up different scents.

Vosshall and her colleagues found 14 genes strongly linked to liking humans, but one odor receptor gene - Or4 - stood out. "It's very highly expressed in human-preferring mosquitoes," Vosshall says.

The researchers guessed that Or4 must be detecting some aroma in human body odor. To figure out which one, they asked volunteers to wear pantyhose for 24 hours. And then they placed those stinky stockings in a machine designed to separate their scent into the hundreds of individual chemicals that make up body odor. The researchers came up with one match, a chemical called sulcatone that was not found in pantyhose worn by guinea pigs.



A comparison of domestic and forest form antennae found that two odorant-receptor genes, Or4 and Or103, are more 'expressed,' or abundant, in the human-preferring domestic mosquitoes (top bar) than in the forest form that feeds primarily on non-human animals (bottom bar). The color scale indicates the level

of gene expression with purple standing for the least amount and red for the most. The numbers to the left of the colored bars represent three different colonies of each mosquito form. The slanted line under each gene's name points to the level of expression of that gene in each colony. Credit: Carolyn McBride, Department of Ecology and Evolutionary Biology and the Princeton Neuroscience Institute

Sulcatone is an important odor that gives humans our distinctive scent, but there are likely other odors and other genes that help explain mosquitoes' attraction to humans. In fact, adding sulcatone to the guinea pig odor didn't make guinea pig scent more appealing to human-loving mosquitoes. McBride, now at Princeton University, plans to look for other factors to help explain how mosquitoes transitioned from harmless animal-biting insects into deadly vectors of human disease.

The switch from preferring animals to humans involves a variety of behavior adjustments: Mosquitoes had to become comfortable living around humans, entering their homes, breeding in clean water found in water jugs instead of the muddy water found in tree holes. "There's a whole suite of things that mosquitoes have to change about their lifestyle to live around humans," Vosshall says. "This paper provides the first genetic insight into what happened thousands of years ago when some mosquitoes made this switch."

More information: Evolution of mosquito preference for humans linked to functional variation in an odorant receptor, *Nature*, DOI: 10.1038/nature13964

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